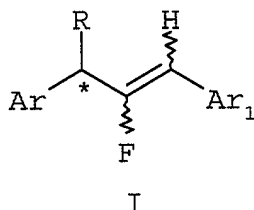


WHAT IS CLAIMED IS:

1. A process for the preparation of a chiral compound of formula I



wherein

Ar is phenyl optionally substituted with any

combination of from one to three halogen,
C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy,
C₁-C₄haloalkoxy or hydroxy groups,

1- or 2-naphthyl optionally substituted with any
combination of from one to three halogen,
C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or
C₁-C₄haloalkoxy groups, or

a 5- or 6-membered heteroaromatic ring optionally
substituted with any combination of from one
to

three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl,
C₁-C₄alkoxy or C₁-C₄haloalkoxy groups;

R is C₁-C₄alkyl, C₁-C₄haloalkyl, C₃-C₆cycloalkyl or
C₃-C₆halocycloalkyl;

Ar₁ is phenoxyphenyl optionally substituted with any
combination of from one to six halogen,
C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or
C₁-C₄haloalkoxy groups,

phenyl optionally substituted with any combination
of from one to five halogen, C₁-C₄alkyl,

C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

biphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

phenoxyphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzylpyridyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzylphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzoylphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

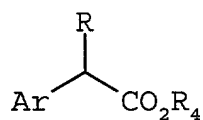
1- or 2-naphthyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, or

a 5- or 6-membered heteroaromatic ring optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, and

the (E)- and (Z)- isomers thereof,

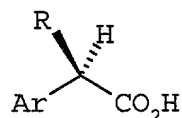
which process comprises the following steps:

a) treating a racemic ester of formula II



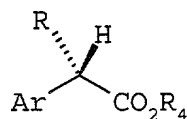
II

wherein Ar and R are defined as hereinabove and R₄ is C₁-C₄alkyl with an esterase to form a first mixture of either R-acid IIIa and S-ester IIIb



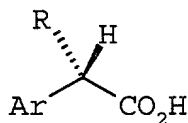
IIIa

and



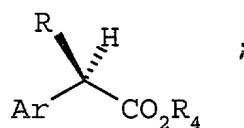
IIIb

or of S-acid IIIc and R-ester IIId



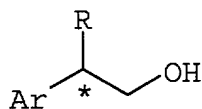
IIIc

and



IIId

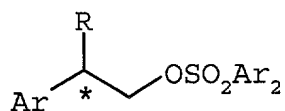
- b) separating said acid IIIa or IIIc from said ester IIIb or IIId;
- c) reducing said acid IIIa or IIIc or said ester IIIb or IIId to obtain a chiral alcohol IV having the R- or S-configuration



IV

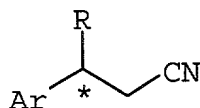
- d) reacting said chiral alcohol with an arylsulfonyl halide Ar₂SO₂X

wherein Ar₂ is phenyl, p-chlorophenyl, or p-tolyl, and X is chloro, bromo or fluoro to afford a sulfonate of formula V



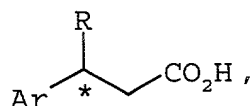
V

e) reacting said sulfonate V with a cyanide-delivering agent to afford a nitrile of formula VI



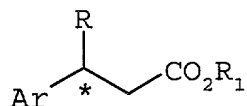
VI

f) hydrolyzing said nitrile VI to afford an acid of formula VII



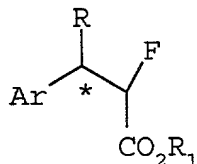
VII

g) esterifying said acid VII with an alcohol R_1OH , wherein R_1 is C_1 - C_4 alkyl to afford an ester of formula VIII



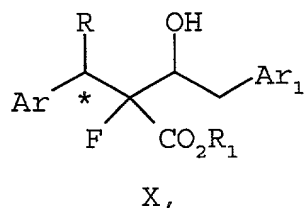
VIII

h) fluorinating said ester to afford a fluoro-ester of formula IX



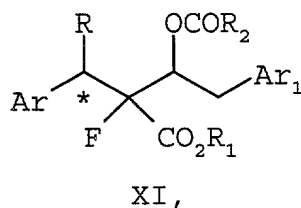
IX

i) reacting said fluoro ester with an aldehyde $\text{Ar}_1\text{CH}_2\text{CHO}$, wherein Ar_1 is defined as hereinabove, in a solvent in the presence of a base to afford a second mixture of 4 chiral diastereomeric hydroxy-esters of formula X;



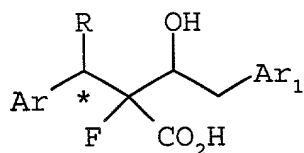
j) optionally separating said second mixture X into a third mixture Xa and a fourth mixture Xb, each mixture having two chiral diastereomers;

k) treating said hydroxy-ester mixture X, Xa or Xb with an acylating agent R_2COX_1 , wherein R_2 is C_1 - C_4 alkyl and X_1 is Cl, Br or R_2COO , to afford a fifth mixture of 4 chiral diastereomeric acyloxy esters XI, a sixth mixture of 2 acyloxy esters of formula XIa, or a seventh mixture of 2 chiral diastereomeric acyloxy esters XIb



l) optionally separating said sixth or seventh mixture into essentially pure chiral diastereomeric acyloxy esters;

m) hydrolyzing said pure chiral acyloxy esters or mixtures of esters of formula XI to afford a hydroxy-acid of formula XII,



XII

and

n) heating said hydroxy-acid XII with an arylsulfonyl halide $\text{Ar}_3\text{SO}_2\text{X}_2$, wherein Ar_3 is phenyl, p-chlorophenyl, or p-tolyl, and X_2 is chloro or bromo to afford the desired chiral compound of formula I.

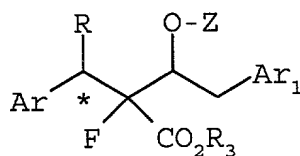
2. The process according to claim 1 wherein said esterase is horse liver esterase.

3. The process according to claim 1 wherein said base is lithium diisopropylamide.

4. The process according to claim 1 wherein said solvent is tetrahydrofuran.

5. The process according to claim 1 wherein R_4 is methyl.

6. A chiral compound of the following formula



XIII

wherein

Ar is phenyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄haloalkoxy or hydroxy groups,
1- or 2-naphthyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, or
a 5- or 6-membered heteroaromatic ring optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups;
R is C₁-C₄alkyl, C₁-C₄haloalkyl, C₃-C₆cycloalkyl or C₃-C₆halocycloalkyl;
Ar₁ is phenoxyphenyl optionally substituted with any combination of from one to six halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,
phenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,
biphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,
phenoxyphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,
benzylpyridyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzylphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzoylphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

1- or 2-naphthyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, or

a 5- or 6-membered heteroaromatic ring optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, and

R₃ is H or C₁-C₄ alkyl; and

Z is H or COR₂, wherein R₂ is C₁-C₄ alkyl.

7. The compound according to claim 6 wherein Ar is phenyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups; and R is C₁-C₄alkyl or C₃-C₆cycloalkyl.

8. The compound according to claim 7 wherein Ar₁ is phenyl optionally substituted with one to three halogen groups; and R is C₃-C₆cycloalkyl.

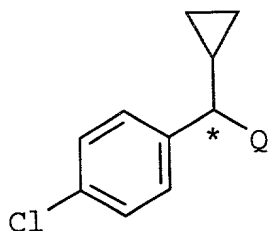
9. The compound according to claim 8 selected from the group consisting of

methyl (2S,3S)-2-[(R)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2R,3R)-2-[(R)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2S,3R)-2-[(R)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2R,3S)-2-[(R)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2S,3S)-2-[(S)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2R,3R)-2-[(S)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2S,3R)-2-[(S)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2R,3S)-2-[(S)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2S,3S)-3-(acetyloxy)-2-[(S)-(4-chlorophenyl)-
 (cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-
 phenoxyphenyl)butanoate;
 methyl (2R,3R)-3-(acetyloxy)-2-[(S)-(4-chlorophenyl)-
 (cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-
 phenoxyphenyl)butanoate;
 methyl (2R,3R)-3-(acetyloxy)-2-[(S)-(4-chlorophenyl)-
 (cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-
 phenoxyphenyl)butanoate;

methyl (2S,3R) -3- (acetyloxy) -2- [(S) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 methyl (2S,3S) -3- (acetyloxy) -2- [(R) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 methyl (2R,3R) -3- (acetyloxy) -2- [(R) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 methyl (2R,3S) -3- (acetyloxy) -2- [(R) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 methyl (2S,3R) -3- (acetyloxy) -2- [(R) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 (2S,3S) -2- [(S) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2R,3R) -2- [(S) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2R,3S) -2- [(S) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2S,3R) -2- [(S) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2S,3S) -2- [(R) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2R,3R) -2- [(R) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;

(2R,3S)-2-[(R)-(4-chlorophenyl)(cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-3-hydroxybutanoic acid; and
 (2S,3R)-2-[(R)-(4-chlorophenyl)(cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-3-hydroxybutanoic acid.

10. A chiral compound of the following formula



wherein

Q is $-\text{CO}_2\text{H}$; $-\text{CO}_2\text{CH}_3$; $-\text{CH}_2\text{OH}$; $-\text{CH}_2\text{OSO}_2\text{Ar}_2$; $-\text{CH}_2\text{CN}$; $-\text{CH}_2\text{CO}_2\text{H}$; $-\text{CH}_2\text{CO}_2\text{R}_1$; or $-\text{CHFCO}_2\text{R}_1$;
 Ar_2 is phenyl, p-chlorophenyl or p-tolyl; and
 R_1 is C_1 - C_4 alkyl.

11. The compound according to claim 10 selected from the group consisting of
 (2R)-2-(4-chlorophenyl)-2-cyclopropylethyl 4-methylbenzenesulfonate;
 (2S)-2-(4-chlorophenyl)-2-cyclopropylethyl 4-methylbenzenesulfonate;
 (3R)-3-(4-chlorophenyl)-3-cyclopropylpropanenitrile;
 (3S)-3-(4-chlorophenyl)-3-cyclopropylpropanenitrile;
 (3R)-3-(4-chlorophenyl)-3-cyclopropylpropanoic acid;
 (3S)-3-(4-chlorophenyl)-3-cyclopropylpropanoic acid;
 methyl (3R)-3-(4-chlorophenyl)-3-cyclopropylpropanoate;
 methyl (3S)-3-(4-chlorophenyl)-3-cyclopropylpropanoate;

Year	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	